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10/559,835	03/08/2006	Takehisa Matsuda	2005_1807A	7978

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
02/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/559,835	MATSUDA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30,32-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *1-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06-19-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of the claims. Claims 1-26, 30, 32-37 and 39-40 are pending. Claims 30 and 37 have been amended by Applicants' amendment filed on 11-02-2009. Claims 1-26 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention. The election was made without traverse in Applicants' responses filed on in the replies filed on 11-05-2007 and 03-06-2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
3. Therefore, claims 30, 32-37 and 39-40 are currently under examination to which the following grounds of rejection are applicable.
4. The examiner acknowledges recording two Declarations under 37 CFR 1.132 signed by Dr. Kunio Matsumoto.

Response to arguments

Withdrawn rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment of claims 30 and 37 to delete the phrase "represented by", rejection of claims 30, 32-37 and 39-40 under 35 U.S.C. 112, second paragraph has been withdrawn.

Applicants' arguments are moot in view of the withdrawn rejection.

Double Patenting

In view of Applicants' amendment of claim 30, objection to claim 37 under 37 CFR 1.75 as being a substantial duplicate of claim 30 has been withdrawn.

Note that the claimed method of claim 30 does not place any limitation on whether the DNA encoding a protein of SEQ ID NO: 4 in a cell-containing preparation is expressed, whereas claim 37 requires for the DNA of sequence ID NO: 2 to express a peptide.

Remaining rejections in response to Applicant arguments or amendments

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 30, 32-37 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

> a method of inhibiting growth, invasion and metastasis of cancer or for exhibiting an antagonistic activity against hepatocyte growth factor (HGF), which comprises administering to a mammal a cell-containing preparation comprising a cell which has a DNA having the base sequence of SEQ ID NO:2, or a DNA encoding a protein having the amino acid sequence of SEQ ID NO:4, a fibrous protein and a mesh sheet comprising a biodegradable resin to a mammal, the cell being an epithelial cell of the oral submucosa or a fibroblast,

does not reasonably provide enablement for other fragments or variants thereof which encode a protein which has an activity equivalent to mature human NK4 protein.

Response to applicant arguments as they relate to rejection of claims 30, 32-37 and 39-40 under 35 U.S.C. 112, first paragraph-scope of enablement

At page 7 of applicants' remarks filed on 11-02-2009, Applicants essentially argue that claims 30 and 37 have been amended to encompass proteins that have a structure similar to SEQ ID No. 2.

The examiner notes that Applicants have amended claims 30 and 37 to delete the phrase "represented by". However, claims 30 and 37 still encompass the full length sequence of the polynucleotide of SEQ ID NO:2 or any portion thereof and the full length sequence of the polypeptide of SEQ ID NO:4 or any portion thereof. Amending the claims to recite ""a cell which has a DNA having the base sequence of SEQ ID NO:2" and "a DNA encoding a protein having the amino acid sequence of SEQ ID NO:4" would overcome the claims rejection under 35 U.S.C. 112, first paragraph .

Claim Rejections - 35 USC § 103

To the extent that claim 30 encompassed on the alternative **"the cell being … a fibroblast", the following rejections are maintained.**

Claims **30, 32, 34-37 and 39** remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) for the reasons already of record as set forth at pages 7-10 of the office action of 06-01-2009.

Response to Applicants' arguments as they apply to rejection of claims 30, 32, 34-37, 39 under 35 USC § 103

At page 8 of the remarks filed on 11-02-2009, Applicants essentially argue that: 1) the method of amended claim 30 is a method for exhibiting an antagonist activity against HGF, no a method for inhibiting angiogenesis, 2) Unlike NK4, angiostatin does not exhibit an antagonist activity against HGF, as proved by § 1.132 Declaration of Dr. Matsumoto (No. 1) attached hereto [Attachment A]; therefore, Folkman does not disclose an *ex vivo* therapy method for exhibiting an antagonist activity against HGF , 3) there is not motivation to transform cells with the cDNA encoding NK4 of Nakamura in the *ex vivo* therapy method of Folkman to exhibit an antagonistic activity against HGF, 4) the claims required a combination of a fibrous protein and biodegradable resin in addition to cells having the NK4 gene which limitation is not taught or suggested by Folkman, and 5) the method of claim 40 exhibits surprising advantageous effects as evidenced by the § 1.132 Declaration of Dr. Matsumoto (No. 2) [Attachment B]. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), note that the preamble of claim 30 is in the alternative, either to inhibiting growth, invasion and metastasis of cancer or for exhibiting an antagonistic activity against HGF. Thus, in contract to applicants' arguments, the claimed invention does not preclude the method of claim 30 to be effective for inhibiting growth or invasion and metastasis of cancer, which functions are not necessarily the same as an antagonistic activity against HGF. Moreover, it is noticed that if the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations,

then the preamble is not considered a limitation and is of no significance to claim construction. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). That is the case here. Thus the preamble of claim 30 is not given patentable weight.

Regarding 2) and 3), the fact that angiostatin does not exhibit an antagonist activity against HGF, as proved by § 1.132 Declaration of Dr. Matsumoto (No. 1) is not disputed. However, as stated in the paragraph above, the preamble of claim 30 is not given patentable weight. Furthermore, the combined teachings of Folkman and Kuba clearly discloses that NK4 no only inhibits angiogenesis induced by angiogenic factors but also functions as is an inhibitor of HGF by antagonizing the c-Met/HGF (Kuba et al, see Abstract, for example). Folkman focuses primarily on angiostatin but also teaches that kringle regions of other proteins, including hepatocyte growth factor (HGF) can be used to inhibit growth and metastasis of cancer. Kuba et al., discloses that human NK4 containing four kringle domains and functions as an anti-tumor agent. Like NK4, angiostatin comprises kringle domains or structures and is a potent angiogenic inhibitor of tumors. Consequently, one would expect that like angiostatin, NK4 *ex vivo* gene therapy treatment would also inhibit tumor growth and metastasis.

Regarding 4), Folkman et al., un mistakably teaches combinations with therapeutic compositions such as collagen matrix (col. 21; lines 10-15, 20 and 28) and matrices made from biocompatible materials such polyglycolide (polymer of glycolic acid) (col. 11, line 53; col. 21,

lines 26-36). Accordingly, the art reads on a combination of a fibrous protein and biodegradable resin in addition to cells having an angiostatin gene.

Regarding 5), the fact that production of NK4 by epithelial cells of oral mucosa into which DNA encoding NK4 has been introduced and is expressed is 44-fold or more greater than that by pancreatic cancer cells, lung carcinoma cells or melanoma cells, as evidenced by § 1.132 Declaration of Dr. Matsumoto (No. 2) is not disputed. However, with respect to applicants' argument that when, "DNA encoding NK4 is infected to various types of cells using adeno-associated virus (AAV) vector, NK4 production of epithelial cells of the oral mucosa is 44-times or more" is not found persuasive because it is noted that the features upon which applicant relies (e.g., DNA encoding NK4 infected and produced in epithelial cells of oral mucosa, Specification, page 24, lines 1-15) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite that epithelial cells of oral mucosa infected with Ad-K4 produce NK4.

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To the extent that **claim 30 and 40** read **on epithelial cells of the oral mucosa that have not been transformed with a recombinant adeno-associated vector** comprising a DNA having the base sequence of SEQ ID NO:2, or a DNA encoding a protein having the amino acid sequence of SEQ ID NO:4 but unable to produce NK4 protein, the following rejection is maintained.

Claims 30 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32 and 34-37 and 39 above, and further in view of Medico et al., , US Patent US 6551991 (Date of Patent, April 22, 2003) and Mooney et al., (US Patent 5,885,829, Date of Patent March 23, 1999) for the reasons already of record as set forth at pages 14-15 of the office action of 06-01-2009 for the reasons already of record.

Note that Applicant has provided a single response that properly applies to the rejection of claims 30, 32, 34-37, 39 under 35 USC § 103 and rejection of claims 33 and 40 under 35 USC § 103, and is equally relevant.

New Claim Objection

Claim 30 is objected to because of the following informalities: abbreviations such as HGF should be spelled out at the first encounter in the claims. Additionally, claim 36 is objected to because the abbreviation "HIV" does not constitute the proper abbreviation of lentivirus. Appropriate correction is required.

References made of record in a PTO-892 Form to complete the record

Matsumoto K, et al., Biochem Biophys Res Commun. 2005 Jul 29;333(2):289-91.

Conclusion

Claims 30, 32-37 and 39-40 are rejected

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633